

## REMARKS/ARGUMENTS

### *Status of Claims*

Claims 1, 7-8, 11-15, 17, 20-21, 24, and 28-29 have been amended; Claims 2-6 have been withdrawn; Claims 9-10, 18-19, 22-23, 25-27, and 30-33 have been canceled; Claims 34-62 have been added. Claims 1, 7-8, 11-17, 20-21, 24, 28-29 and new Claims 34-62 remain pending. Applicants hereby request further examination and favorable reconsideration of the current claims as amended.

### **The 35 U.S.C. Section 112, Second Paragraph Rejection of Claims 1 and 25**

Claims 1 and 25 have been rejected under 35 U.S.C. Section 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 25 has been canceled and thus the rejection is moot.

Claim 1 has been amended to include the step of assessing the propensity for patient risk, as the Examiner suggested, and thus Applicant believes it is now in proper form.

### **The 35 U.S.C. Section 112, First Paragraph Rejection of Claims 1, 7, 8, 13-17, and 22-25**

Claims 1, 7, 8, 13-17, and 22-25 have been rejected under 35 U.S.C. Section 112, First Paragraph, on the grounds that the specification does not reasonably provide enablement for determining thrombotic disease risks using any and all clotting assays. Claims 22-23 and 25 have been canceled for other reasons since they are unnecessary in view of the amendments to other claims. Applicants respectfully traverse this rejection as to the remaining claims.

Claim 1 has been amended to recite an improvement to an assay in which activated protein C is used and the phospholipid comprises phosphatidylethanolamine and phosphatidylserine the only required phospholipid component (as seen in U.S. Patent 5,372,852, for example, which was incorporated herein by reference (page 6, lines 19-19), phosphatidylcholine need not be a required part of the reagent).

Claim 7 is only directed to an assay for determining if a sample contains the antibodies which selectively block oxidized phospholipids. It has been amended to recite the composition of the phospholipid reagent. Accordingly, the rejection of claim is traversed for the additional reason that it is a test for antibodies, and not specifically a test for assessing the risk for thrombotic disease. The specification provides guidance for how to make and how to use the claimed invention, which is all that is required for enablement. The Applicants' invention is a conception that in assays which test clotting, one can now vary the phospholipids reagent and make certain conclusions based on a comparison of the result with oxidized phospholipids on the one hand and non-oxidized on the other. Since this is the variance taught by Applicants, one will always have at least two results which are to be compared directly to one another. One of the two will test the clotting time with oxidized phospholipids and the other of the two will test the clotting time with non-oxidized phospholipids. Thus, there is a built-in control, and Applicants are entitled to claim varying any clotting assay by this one parameter.

Claim 8 is directed to the assay of Claim 7 with additional steps. The rejection of Claim 8 for lack of enablement is respectfully traversed since it is not directed to a method for making an assessment of thrombotic disease risk but rather detection of antibodies.

Claim 13 does contain language with respect to determining propensity for a thrombotic episode. It has been amended to specify the composition of the phospholipid reagent. Otherwise, the rejection is respectfully traversed, since all that is required for enablement is that the specification tells how to make and to use the claimed invention. The specification does provide how to conduct the assay and the claim recites how to conclude whether or not increased risk of thrombotic episodes is present. The propriety of the clotting assay recitation has been addressed above.

Claims 14-17 and 22-25 are ultimately dependent on Claim 13. Claims 22, 23 and 25 have been canceled for other reasons. The rejection as to the remaining claims is respectfully traversed on the same grounds as stated for claim 13.

The Examiner's Action contained the following further comments:

That the invention is directed to determining risk of thrombotic disease by performing a coagulation assay with and without the presence of oxidized phospholipids containing PE and comparing the results. Applicants interpret the Examiner's remarks to indicate that if the claims were amended to recite that the phospholipids reagents comprise PE, the claims would be considered properly enabled. This amendment has been made, and thus it is believed that the Examiner's rejection has been properly met.

The Examiner comments that the claims are directed to the performance of any coagulation test, and this is true as long as the coagulation test employs activated protein C or at least tests for a baseline without activated protein C in comparison to results with activated protein C (Claim 8). Claim 7 now recites that if the enhanced anticoagulant effect of activated protein C in the presence of oxidized phospholipids is blocked (Spec. p. 5, l. 9-10.), that is an indication of blocking antibodies. If a coagulation test in the presence of activated protein C employs a phospholipid reagent that permits clotting, then Applicants invention involves improving that test by first changing the oxidation of that reagent, and secondarily modifying the composition of phospholipids, in order to obtain results which provide more information on the propensity for thrombotic disease risk.

#### **Amount of Guidance and Working Examples**

The Examiner indicates that from the specification, the assay must contain PE to work. The claims have now been amended to specify that the phospholipid reagents comprise PE, and also PS of which an effective amount is required to compliment the function of PE.

The Examiner states that undue experimentation would be required to practice the invention as claimed. Applicants respectfully traverse this determination.

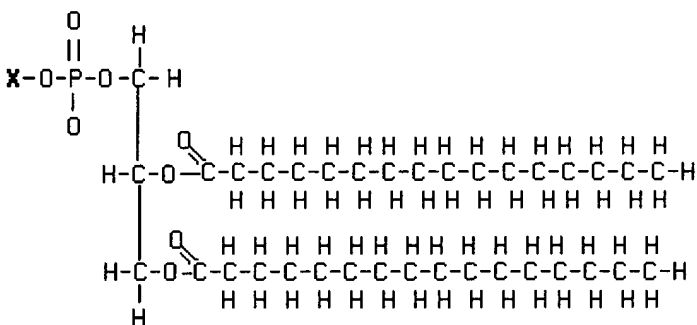
The Applicants have provided in the Specification how to make and how to use the invention. The invention is clearly recited in the claims – one uses a reagent containing PE and compares the results of identical assays which vary only in whether the reagent is oxidized or

not. The specification explains how to make the reagents. The claims now have been amended to recite how one concludes there is a propensity for thrombotic disease. Nothing more is required under the law, and Applicants have fulfilled the enablement requirement.

### **The 35 U.S.C. Section 102 Rejection of Claims 1, 7, 9-11, 13 and 18-20**

In the portion of the Official Action concerning enablement, the Examiner stated, “There does not appear to be any prior art directed to the intended determination of propensity of patient risk for thrombotic disease or determination of antibodies which selectively block the action of oxidized lipids.

Here, the Examiner has rejected Claims 1, 7, 9-11, 13, and 18-20 under 35 U.S.C. §102(b) as being clearly anticipated by Aviram et al., “Oxidized low density lipoprotein reduces plasma coagulation *in vitro*”, *Scan. J. Clin Lab Invest*; 51:17-21 (1991) Claims 9-10, and 18-19 have been cancelled for other reasons. Claims 1, 7, 11, 13, and 20 have been amended to better specify the composition of the reagents. Applicants respectfully traverse the Examiner’s rejection as to the claims as amended. Aviram studied the effect of lipoproteins (emphasis added) on coagulation, not phospholipids as are used by Applicants’ invention. Lipoproteins are a complex globular structure composed of an outer protein envelope and a lipid core. Phospholipids, in contrast, contain glycerol, two fatty acids, a phosphate, and



a polar molecule, “X”, such as ethanolamine, serine, or choline in a structure such as is shown above and no protein. Aviram found that when lipoprotein was oxidized, it prolonged the coagulation time in two clotting tests: prothrombin time and partial thromboplastin time as compared with non-oxidized lipoprotein. Aviram also reported that it was the apo-protein

portion of the lipoprotein that caused this effect to occur, not the lipid portion. He showed this by delipidation of the lipoprotein and retesting. Since Aviram used a different entity, a lipoprotein rather than a phospholipid, and Aviram discloses nothing about making a determination as to whether a patient has antibodies that block the action of oxidized phospholipids, Aviram does not anticipate Applicants invention as claimed in Claims 1, 7, 10-11, 13, and 19-20. Aviram also does not render Applicants invention obvious, since from Aviram's teachings one would conclude that oxidation of a lipid, as contrasted with a lipoprotein, does not affect coagulation.

Therefore, Applicants respectfully request that the Claims as amended be reconsidered and allowed.

#### **Allowable Subject Matter**

Applicants note with appreciation the Examiner's indication that Claims 12, 21, and 26-33 contain allowable subject matter. Applicants have now amended Claim 7 on which Claim 12 ultimately depends, Claim 13, on which Claim 21 and old Claims 26-33 ultimately depended, to include a recitation of phosphatidylethanolamine (PE) and phosphatidylserine as required ingredients of the phospholipid reagent. Therefore, Claims 26-27, 30-33 have been canceled as they refined the prior claims with the identification of PE or PS and this is unnecessary in view of the amendments to the other claims. The dependencies of Claims 12, 21 and 28-29 have been changed to reflect the option of adding PC to the reagent that must contain PE and PS. Therefore, it is believed that the amendments place all pending claims in condition for allowance.

#### **Other Amendments, Added Claims**

The specification has been amended to specifically include language supporting new Claims 50-54 from U.S. Patent No. 5,472,853 to Smirnov et al., Col. 6, lines 40-45 which was incorporated by reference into the pending application on page 6, lines 15-19 of the specification.

Claim 15 has been amended in accordance with the specification, p. 6, line 27 to specify the immunoglobulin can be obtained from patient serum. It has also been amended to refer only to Claim 13, since it was believed to be more proper to present a separate series of claims concerning the immunoglobulin fraction. (New Claims 61 and 62.)

Claim 17 has been amended in accordance with the specification, p. 7, lines 3-12 to clarify that the concentration of the immunoglobulin is the assay concentration. It now refers to new Claim 61 due to the amendment to Claim 15.

New Claims 36-44 recite specific embodiments of the phospholipid reagent set forth in the specification (p. 7, l. 13 – p.8, l. 15) and New Claims 50-54 recite the preferred clotting initiating substance (p. 10, l. 27) and U.S. Patent 5,472,853, Col. 6, lines 40-45 which was incorporated by reference into the present specification and has now been specifically inserted in this Amendment.

New Claims 55-60 add dependent claims to Claims 7-8 to parallel Claims 14-17, and new Claims 61 and 62, which ultimately depend on Claim 13. These are believed to be clearer and in better form, since unamended Claim 15 referred to an immunoglobulin fraction not recited in Claim 13.

## CONCLUSION

A request for a one month extension of time for responding to the Office Action mailed June 17, 2004 is respectfully requested and attached hereto. Consideration of the foregoing amendments and remarks, reconsideration of the application, and withdrawal of the rejections and objections is respectfully requested by Applicants. No new matter is introduced by way of the amendment. It is believed that each ground of rejection raised in the Office Action dated June 17, 2004 has been fully addressed. The Commissioner is hereby authorized to charge any fees associated with this paper or credit any overpayment to Deposit Account Number 50-1515 of Conley Rose, P.C., Texas.

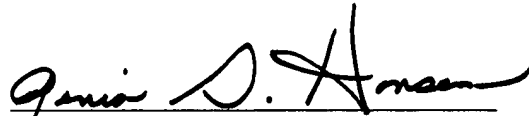
If a telephone conference would facilitate the resolution of any issue or expedite the prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,

CONLEY ROSE, P.C.

Date: October 18, 2004

5700 Granite Parkway, Suite 330  
Dallas, Texas 75024  
Telephone: (972) 731-2288  
Facsimile: (972) 731-2289

  
Eugenia S. Hansen  
Reg. No. 31,966  
ATTORNEY FOR APPLICANTS